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Ethyl 2-Cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY): A Recyclable Coupling Reagent for Racemization-Free Synthesis of Peptide, Amide, Hydroxamate, and Ester

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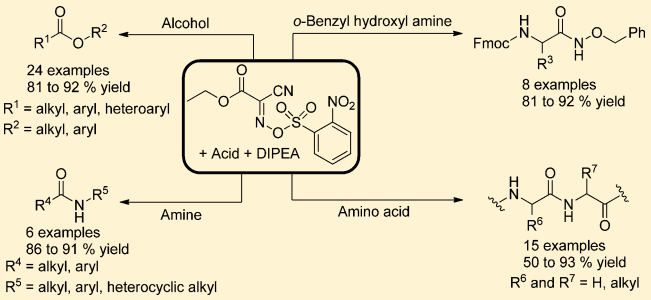
Supporting Information

ABSTRACT: Ubiquitousness of amide and ester functionality makes coupling reactions extremely important. Although numerous coupling reagents are available, methods of preparation of the common and efficient reagents are cumbersome. Those reagents generate a substantial amount of chemical waste and lack recyclability. Ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY), the first member of a new generation of coupling reagents, produces byproducts that can be easily recovered and reused for the synthesis of the same reagent, making the method more environmentally friendly and cost-effective. The synthesis of amides, hydroxamates, peptides, and esters using this reagent is described. The synthesis of the difficult sequences, for example, the islet amyloid polypeptide (22−27) fragment (with a C-terminal Gly, H-Asn-Phe-Gly-Ala-Ile-Leu-Gly-NH_2) and acyl carrier protein (65−74) fragment (H-Val-Gln-Ala-Ala-Ile-Asp-Tyr-Ile-Asn-Gly-OH), following the solid-phase peptide synthesis (SPPS) protocol and Amyloid β (39−42) peptide (Boc-Val-Val-IIe-Ala-OMe), following solution-phase strategy is demonstrated. Remarkable improvement is noticed with respect to reaction time, yield, and retention of stereochemistry. A mechanistic investigation and recyclability are also described.



INTRODUCTION

Amide and ester functionalities are present in most natural products as well as pharmaceutical compounds.[1] Therefore, coupling reactions, which comprise activation of carboxylic acids into an activated form that undergo acylation to produce esters, amides, and peptides, are extremely important for academia and industry. Numerous coupling reagents have been developed and commercialized including carbodiimides, phosphonium, and uronium/aminium salts.[2] Most of them engage the benzotriazole or azabenzotriazole ring system as an important fragment of their structure, which is subsequently transformed into a good leaving group.[3] After two decades of domination of benzotriazole-based chemistry, with the pioneering work of Albericio et al., a new class of peptide coupling reagents, that is, ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma)-based reagents, have been introduced.[4] Oxyma is superior to its counterparts as a racemization suppressant and environmentally friendly reagent.[5] Nevertheless, existing popular coupling reagents (HOBt based coupling reagents as well as Oxyma-based coupling reagents) still suffer from three major drawbacks: (a) They generate lot of chemical waste. For example, carcinogenic hexamethylphosphoramide (HMPA) and explosive hydroxybezotriazole (HOBt) are generated as byproducts when benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate (BOP) is used as coupling reagent.[6] Similarly, a urea derivative as well as HOBt is generated when *N*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluoro phosphate (HBTU) is used.[7] (b) Preparation protocols of these reagents involve harsh conditions and toxic reagents. For example, HBTU is synthesized using phosgene (inflammable, causes skin damage) and HOBt (explosive) in carbon tetrachloride, a carcinogenic solvent.[7] Similarly, 1-[(1-(cyano-2-ethoxy-2-oxoethylideneaminooxy)dimethylamino-morpholinomethylene)] methanaminium hexafluorophosphate (COMU), an Oxyma-based coupling reagent, is also synthesized using phosgene. (c) Furthermore, recycling those reagents may be cumbersome. Thus, they are not environmentally friendly or cost-effective. Therefore, invention of an ideal coupling reagent with a high level of efficacy but devoid of epimerization tendency while being environmentally friendly and recyclable still remains a challenge. We describe herein a coupling reagent, ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxy-imino)acetate (*o*-NosylOXY, **I**) (Figure 1), which has similar efficiency but is devoid of the said drawbacks.

RESULTS AND DISCUSSION

The reagent **I**, *o*-NosylOXY, was synthesized easily by the reaction between *ortho*-nitrobenzenesulfonyl chloride and Oxyma in the presence of diisopropylethylamine (DIPEA) under nitrogen atmosphere.[8] Reagent **I** is stable at room

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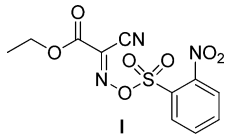
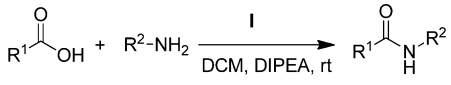


Figure 1. Ethyl 2-cyano-2-(2-nitrobenzenesulfonyloxyimino)acetate (*o*-NosylOXY, **I**).

temperature (25 °C) and can be stored for long time. A time dependent HPLC and ^{1}H NMR studies of **I** indicated no change until 20 days (Supporting Information, Figure S112–S117). Its coupling efficiency was investigated using the reaction between phenyl acetic acid and benzyl amine, DCM as a solvent (Scheme 1). Very good yield (91%) of the product,

Scheme 1. Synthesis of Amides and Peptides Using Reagent I



R^1 = aryl, alkyl, *N*-protected amino acid
R^2 = aryl, alkyl, heterocyclic alkyl or *C*-protected amino acid

N-benzyl-2-phenylacetamide, was obtained in 2 h at room temperature. Sulfonamide formation is an expected side reaction for such reagents. We performed a model reaction between phenylacetic acid and benzyl amine using *o*-NosylOXY in the presence of DIPEA in DCM without preactivation. After completion of the reaction, we found 40% yield of *N*-benzyl-2-nitrobenzenesulfonamide and 50% yield of *N*-benzyl-2-phenylacetamide. To avoid such sulfonamide formation, we used 3–5 min preactivation.

For solvent optimization we screened several solvents for the coupling reaction between phenylacetic acid and benzylamine employing reagent **I**, and DCM was found to be the best solvent (Table 1). Therefore, DCM was used for amidation, esterification, and hydroxamate synthesis.

Table 1. Solvent Screening Experiments

entry[a]	solvent	yield[b] (%)	time (h)
1	acetonitrile	67	8
2	DMSO	56	11
3	THF	48	13
4	DMF	85	3
5	DCM	91	2.2
6	ethyl acetate	70	5
7	chloroform	78	3

[a]Performed with phenylacetic acid (136 mg, 1 equiv), reagent **I** (1 equiv), DIPEA (2.2 equiv), benzylamine (1 equiv), room temperature (25 °C). [b]Yields refer to the isolated yield after column chromatography.

For racemization studies, we synthesized Z-DL-Phe-L-Ala-OMe and Z-L-Phe-L-Ala-OMe using **I** and compared their HPLC profiles (Figure 2) to estimate the amount of racemization caused by the coupling reagent. Appearance of the twin peak in the HPLC profile of Z-DL-Phe-L-Ala-OMe corresponds to the two diastereomeric products, whereas presence of the single peak in that of Z-L-Phe-L-Ala-OMe indicates that virtually no racemization occurred during the synthesis. Comparison of the ^{1}H and ^{13}C NMR spectra of these

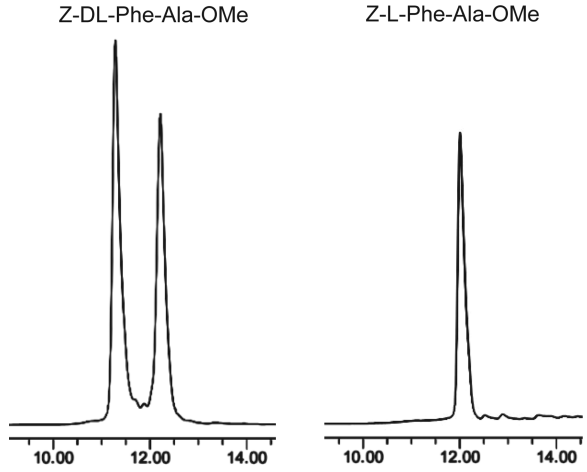


Figure 2. Comparison of the HPLC profiles of Z-DL-Phe-L-Ala-OMe (left panel) and Z-L-Phe-L-Ala-OMe (right panel) (C18 reversed-phase analytical column, 5 μm, 25 cm × 4.6 mm, linear gradient of 0–80%, 0–7 min then 80–100% up to 20 min, CH_3CN in H_2O with 0.1% formic acid).

dipeptides also supports the hypothesis (Supporting Information, Figure S29–S32). We found two doublets in ^{1}H NMR at δ = 1.32 and 1.21 ppm and similarly four peaks at δ = 173.0, 172.9, 170.9, and 170.7 ppm in ^{13}C NMR of Z-DL-Phe-L-Ala-OMe, which indicate the presence of two diastereomers. We also found one doublet at δ = 1.32 ppm in the ^{1}H NMR and two peaks at δ = 173.0 and 170.7 ppm in ^{13}C NMR for Z-L-Phe-L-Ala-OMe, indicating the presence of one diastereomer.

However, suppression of epimerization is known to occur for the presence of the *N*-terminal urethane protecting group.[9] To remove that doubt, we synthesized a tripeptide, Z-Gly-Phe-Val-OMe (entry 18, Table 3), via coupling of Z-Gly-Phe-OH and H-Val-OMe in solution using **I**, estimated the amount of racemization, and compared that with reported data obtained for the synthesis of the same tripeptide using other coupling reagents, such as HBTU (*N*-[(1*H*-benzotriazol-1-yl)(dimethylamino)methylene] *N*-methylmethanaminiumhexafluorophosphate *N*-oxide), HATU (*N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl-methylene)-*N*-methylmethanaminium hexafluorophosphate *N*-oxide), HDMB (1-((dimethylamino)(morpholino)methylene)-1*H*-benzotriazolium hexafluorophosphate 3-oxide), and HDMA (1-((dimethylamino)-(morpholino)methylene)-1*H*-[1,2,3]triazolo[4,5-*b*]pyridinium hexafluorophosphate 3-oxide).[10] No racemization could be observed, when reagent **I** was used, however, epimerization was noted for other reagents (Table 2).

With the suitable conditions in hand, applicability of this method was explored with various carboxylic acids and amines (Table 3). Interestingly, the reaction worked well with aromatic and aliphatic carboxylic acids (entries 1–4, Table 3) as well as amino acids (entry 5–18). Even in the case of a less nucleophilic amine, aniline (entry 4), the yield was found to be remarkably good. However, repeated attempt to perform the reaction with 4-nitroaniline failed. It tolerated common amine protecting groups including Fmoc and Cbz. Furthermore, the reaction worked well for sterically hindered amino acids, e.g., Val (entries 10) and Aib (entries 16 and 17), as the carboxylic acid component as well as tertiary butylamine (entry 6), Aib (entry 7), and Val (entry 18) as the amine component, which are known to be difficult for coupling. In all cases, the yields

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Table 2. Comparison of Yield and Racemization Tendency for the Formation of Z-Gly-Phe-Val-OMe Using *o*-NosylOXY (I) with the Reported[10] Results Using Various Coupling Reagents

entry	coupling reagent	yield (%)	racemization (%)
1	HBTU	89	5.9
2	HATU	90	1.6
3	HDMB	90	2.9
4	HDMA	90	0.7
5	*o*-NosylOXY	91	n.d.[a]

[a]No racemization could be detected by the ^{1}H and ^{13}C NMR spectra and the HPLC profile (Supporting Information, Figures S39−S40 and S128) within the limit of our experimental conditions.

were excellent and comparable with other reported common coupling reagents[11] with no observed racemization.

We also performed the reaction between Fmoc-Phe-OH and NH_2-Ala-OMe in the presence of *o*-nitrobenzenesulfonyl chloride as a coupling reagent. In this case, we obtained dipeptide Fmoc-Phe-Ala-OMe in 65% yield and sulfonamide the , *o*-nitrobenzenesulfonamide of the methyl ester of alanine, in 10% yield. About 10% racemization was observed in the HPLC profile of the dipeptide (Supporting Information, Figures S130−S132). This demonstrates the utility of the Oxyma part in reagent **I**.

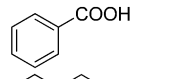
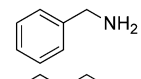
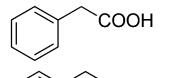
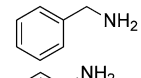
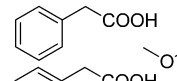
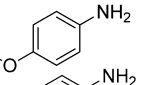
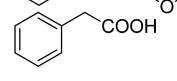
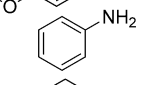
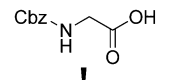
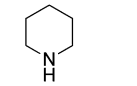
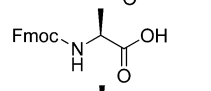
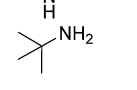
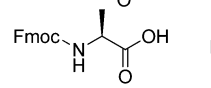
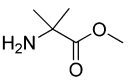
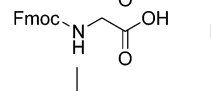
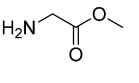
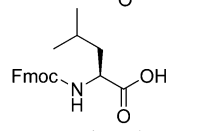
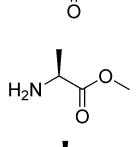
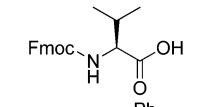
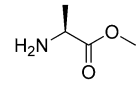
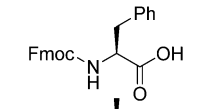
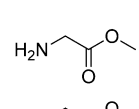
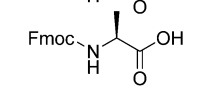
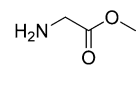
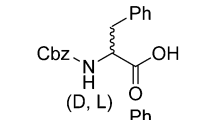
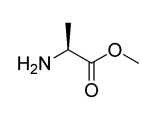
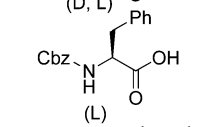
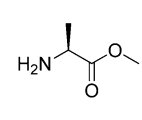
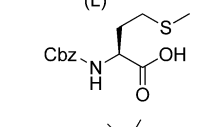
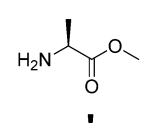
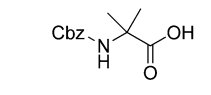
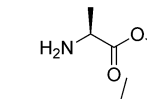
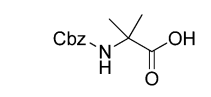
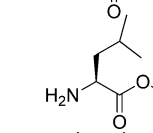
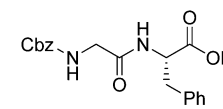
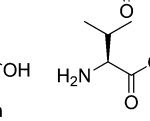
Hydroxamates of amino acids are another interesting class of compounds which possess a broad spectrum of medicinal properties.[12] Therefore, we wanted to adopt the present methodology for the synthesis of such important drug candidates.

Our initial trials of coupling with model substrate, i.e., benzoic acid with *O*-benzylhydroxylamine using reagent **I**, yielded the desired product in very good yield (92%, entry 1, Table 4). It was then further extended to a variety of amino acids with varying side chain complexity (entry 4−8, Table 4). Very good yields (81−91%) were obtained on stirring at room temperature (25 °C) for 2−3 h.

We further envisaged using reagent **I** for long-chain peptide synthesis. As target, we took IAPP (22−27) peptide (IAPP, islet amyloid poly peptide: H-Asn-Phe-Gly-Ala-Ile-Leu-Gly-NH_2, Figure 3a)[13] and ACP (65−74) peptide fragment (ACP, acyl carrier protein: H-Val-Gln-Ala-Ala-Ile-Asp-Tyr-Ile-Asn-Gly-OH, Figure 3b).[11] Both of them are known to be difficult sequences for synthesis as they contain many hydrophobic amino acids and undergo conformational changes resulting in aggregation during the synthesis.

We achieved the synthesis of these peptides in very good yield (40% for the IAPP (22−27) and 50% for the ACP (65−74) fragment after chromatographic purification, with respect to resin loading) by stepwise coupling of constituent amino acids on rink amide MBHA resin using **I** as a coupling reagent following the Fmoc/tBu orthogonal protection technique based SPPS (solid phase peptide synthesis) method. A 3.2-fold excess of the Fmoc amino acids and 3-fold excess of the coupling reagents were used for each coupling step and gently rotated. Care should be taken not to use more of the coupling reagent than the *N*-protected amino acid, unlike other coupling reagents, to avoid truncation by sulfonamide formation. Although reagent **I** generates a higher yield in DCM than in DMF (Table 1), we used DMF as solvent for SPPS, as DMF is more commonly used in SPPS. Couplings were accomplished smoothly in 2 h, which were confirmed by Kaiser test. A small

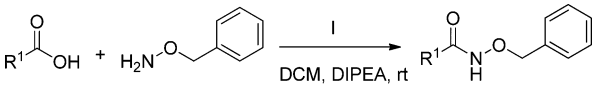
Table 3. Synthesis of Various Amides and Peptides under Optimized Conditions Using Reagent I

Entry[a]	Acid	Amine	Yield (%)[b]
1			88
2			91
3			82
4			86
5			89
6			81
7			80
8			91
9			89
10			87
11			93
12			87
13			90
14			91
15			89
16			81
17			78
18			91

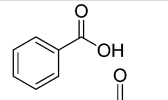
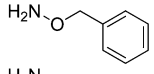
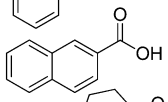
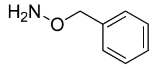
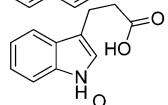
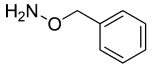
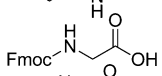
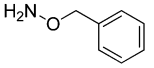
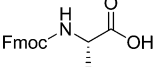
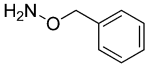
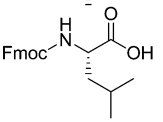
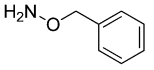
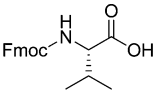
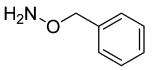
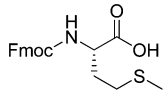
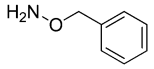
[a]Performed with acid (1 equiv), reagent I (1 equiv), DIPEA (2.2 equiv), amine (1 equiv), room temperature (25 °C), 2−3 h. [b]Yields were referred to the isolated yields after column chromatography.

dx.doi.org/10.1021/jo500292m | J. Org. Chem. 2014, 79, 5420−5431

Table 4. Synthesis of Hydroxamates Using I



R^1 = aryl, alkyl or fmoc-amino acid

Entry[a]	Acid	O-benzylhydroxylamine	Yield (%)[b]
1			92
2			90
3			89
4			91
5			88
6			84
7			82
8			81

[a]Performed with acid (1 equiv), reagent I (1 equiv), DIPEA (2.2 equiv), *O*-benzylhydroxylamine (1 equiv), room temperature (25 °C), 2−3 h. [b]Yields were referred to the isolated yields after column chromatography.

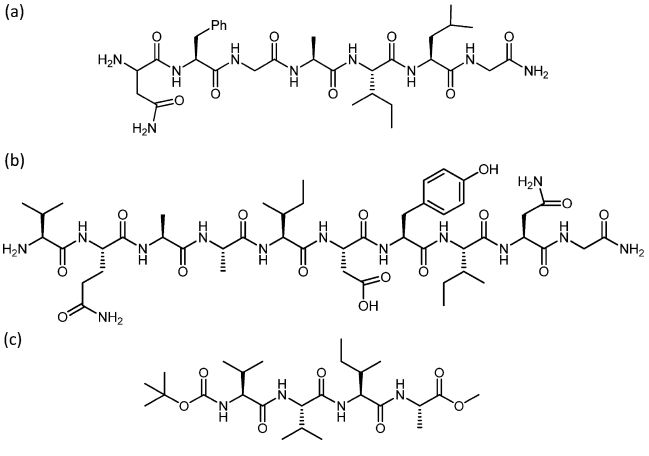


Figure 3. Sequences of peptides synthesized: (a) NFGAILG and (b) VQAAIDYING using SPPS, HPLC, and ESI-MS spectra (see the Supporting Information, Figures S167 and S168); (c) Boc-VVIA-OMe in solution.

amount of resin was taken after each coupling, and the peptide was cleaved from the resin using a TFA/DCM/H_2O mixture, precipitated using cold ether, and injected in analytical HPLC for examining the purity at each step. Each time a single peak was observed, eluent was collected and injected in ESI-MS to confirm the mass of the peptide fragment. The HPLC retention times and ESI-MS data for each fragment during the synthesis of IAPP (22−27) are mentioned in Table S1 (Supporting Information). The HPLC profiles and ESI-MS spectra of the purified peptides are also provided in the Supporting Information (Figures S153 and S154). The quality of the crude peptide also was excellent. As an example, that for peptide ACP (65−74) was compared with the reported data (Table 5).[11] The quality of the crude IAPP (22−27) peptide

Table 5. Comparative Study of the Purity of Crude ACP (65-74) by TBTU, HATU, TBCR, and *o*-NosylOXY

coupling reagent	purity of crude ACP (65−74) (%)
TBTU	69
HATU	87
TBCR	84
o-NosylOXY	90[a]

[a]90% purity of the crude peptide could be detected by HPLC (Supporting Information, Figure S165).

fragment synthesized using **I** as coupling reagent was also very good (Supporting Information, Figure S151). We also synthesized Boc-Val-Val-Ile-Ala-OMe, the C-terminal fragment of the amyloid β peptide.[14] This is also a difficult hydrophobic sequence with huge steric hindrance (Figure 3c). A Boc-chemistry-based stepwise coupling was performed in DCM following solution-phase methodology. The yield was good (78%, after five steps with respect to starting Boc-Ile-OH), and the HPLC chromatogram of the crude peptide (Supporting Information, Figure S137) was as good as a purified peptide.

After completion of the establishment of the applicability of the coupling reagent **I** for the synthesis of amides, hydroxamates, and peptides, we investigated its efficiency for esterification (Scheme 2). In spite of the numerous methodologies for the coupling reaction of alcohols and carboxylic acids, it is still desired to develop an efficient coupling reagent for the said transformation that is racemization free, with high yields for complicated substrates, gives clean isolation of the products, and most importantly, is recyclable. Esterification using **I** addressed most of these difficulties that were associated with the rest of the methodologies.

Scheme 2. Synthesis of Ester under Optimized Conditions

R^1 = aryl or alkyl
R^2 = aryl or alkyl

As a model reaction, we took phenylacetic acid (1 mmol) in dichloromethane and added diisopropylethylamine (1.1 mmol) to it. *o*-NosylOXY (1 mmol) was added to this mixture at room temperature (25 °C) with stirring. After 5 min, benzyl alcohol (1 mmol) and DIPEA (1.1 mmol) were added. After 2 h, the reaction was found to be complete and furnished the desired product in very good yield (92%).

After standardization of the reaction conditions, we investigated the generality of the present protocol by applying it to various alcohols and carboxylic acids. The reaction of phenylacetic acid with varieties of aromatic (entries 1−4, Table 6) and aliphatic (entries 5−7) alcohols worked well. From the observation of the yields of entries 1−4, it was evident that the

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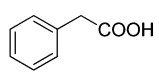
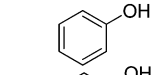
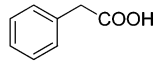
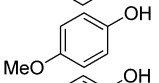
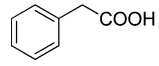
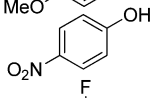
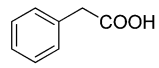
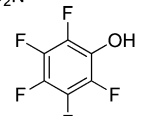
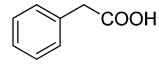
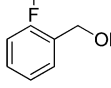
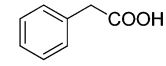
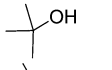
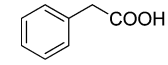
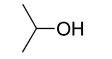
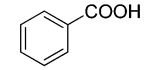
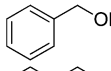
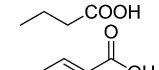
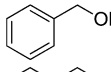
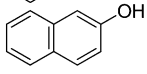
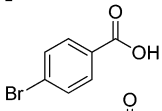
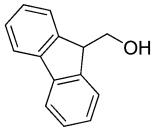
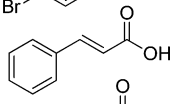
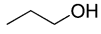
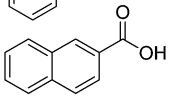
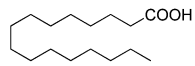
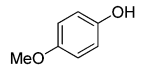
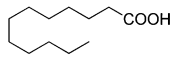
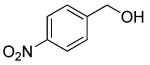
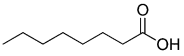
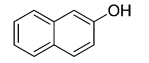
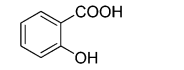
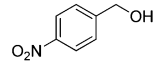
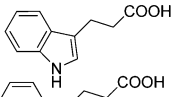
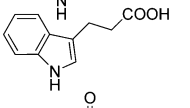
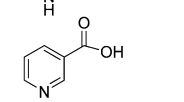
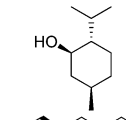
Table 6. Scope of Esterification Using Reagent I

Entry[a]	Acid	Alcohol	Yield(%)[b]
1			87
2			82
3			90
4			81
5			92
6			84
7			89
8			85
9			91
10			90
11			89
12			91
13			87

[a]Performed with acid (1 equiv), reagent **I** (1 equiv), DIPEA (2.2 equiv), alcohol (1 equiv), room temperature (25 °C), 2−3.5 h. [b]Yields refer to the isolated yields after column chromatography.

Table 7. Synthesis of Various Carboxylic Esters Using I

Entry[a]	Acid	Alcohol	Time (h)	Yield (%)[b]
1			4.0	86
2			2.5	92
3			3.0	91
4			2.0	82
5			2.5	86
6			3.0	90
7			3.0	90
8			3.15	89
9		CH_3OH	3.0	87
10			2.5	90
11			2.5	89

[a]Performed with acid (1 equiv), reagent I (1 equiv), DIPEA (2.2 equiv), alcohol (1 equiv), room temperature (25 °C). [b]Yields refer to the isolated yields after column chromatography.

presence of an electron-donating group on phenol retards the reaction and therefore yields less product than its counterparts, which is in agreement with the stability of the phenoxide ions. The reaction proceeded well with secondary (entry 7) and tertiary alcohols (entry 6).

The present protocol was successfully applied for the synthesis of biologically active esters also. The aliphatic carboxylic acids (entries 1−3, Table 7) worked well. The aforementioned electromeric affect holds true for these reactions as well. In case of salicylic acid, i.e., entry 4, the reaction was chemoselctive and produced the 4-nitrobenzyl ester of salicylic acid as a major product, although two nucleophilic attacks were logically possible. Self-condensation was lower due to the lesser nucleophilicity of the hydroxyl group of the salicylic acid than that of the *p*-nitrobenzyl alcohol. Phenolic acids have been esterified with excellent chemoselectivity in the presence of strong protic acids (Fischer esterification), but harsh reaction conditions and an excess of alcohol was required to drive the reaction to a satisfactory degree of conversion,[15] whereas it worked smoothly in the present protocol, which is milder. Furthermore, in the case of entries 5 and 6 (Table 7), the product observed was the ester alone, not the corresponding amide. Various aliphatic primary alcohols (entries 4−11, Table 7) and a secondary alcohol (entry 7) were subjected to the reaction conditions and the yield was good (82−90%).

Even amino acids (entry 9−11, Table 7) retained the same reactivity toward this reaction. In order to estimate the extent of racemization, we initially synthesized Boc-DL-Phe-OBn using our protocol and passed through a chiral column. Two distinct peaks, corresponding to the two enantiomers, were observed in the HPLC chromatogram (Figure 4, left panel). Next, we synthesized Boc-L-Phe-OBn following the same strategy. The chromatographic signature of Boc-L-Phe-OBn reveals only one peak corresponding to the enantiopure product (Figure 4, right panel). Therefore, it was inferred that the present protocol does not cause any detectable racemization.

A plausible mechanism is depicted in Scheme 3. Initially, the nucleophile generated by the deprotonation of the carboxylic acid in the presence of DIPEA attacks the sulfonyl center of **I**. Expulsion of the resonance-stabilized Oxyma anion **II** results in the mixed anhydride **III**. Further nucleophilic attack of **II** on the carbonyl carbon of **III** and expulsion of the sulfonic acid **IV** results in the formation of the intermediate **V**, the activated Oxyma ester of the carboxylic acid. **V** undergoes nucelophilic substitution to produce the corresponding ester or amide.

dx.doi.org/10.1021/jo500292m | J. Org. Chem. 2014, 79, 5420−5431

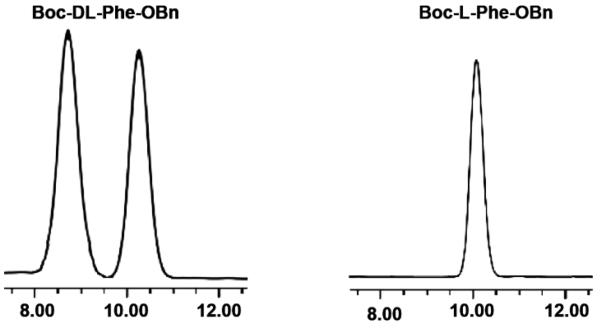
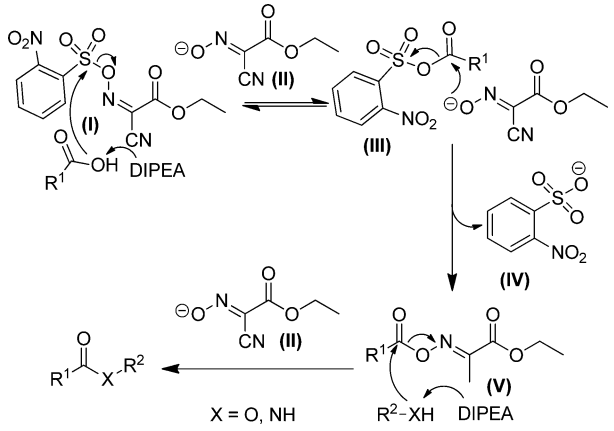


Figure 4. HPLC chromatogram of Boc-D,L-Phe-OBn (left panel) and Boc-L-Phe-OBn (right panel, CHIRAL PAK^{R} AS-H column, 5 μm, 2.1 × 150 mm, an isocratic gradient of 10% 2-propanol in hexane was used).

Scheme 3. Plausible Pathways for the Condensation

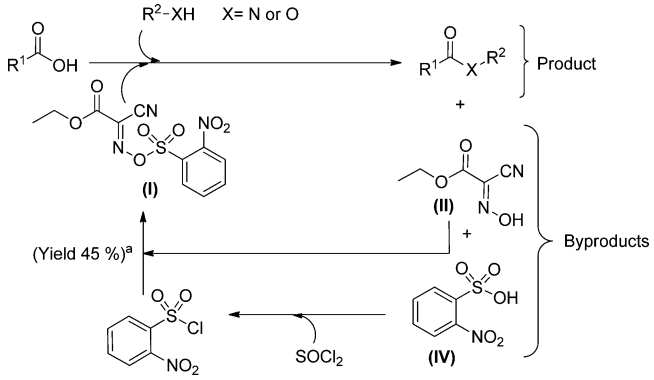


Isolation and complete characterization using ^{1}H NMR and ^{13}C NMR (Supporting Information, Figures S1 and S2) and XRD analysis of the intermediate **V** was achieved (Supporting Information, Figure S169). However, the added nucleophile (amine or alcohol) may also react with the intermediate **III**. In that case, sulfonamide also may get generated as byproduct and racemization of the product is expected, as it was observed when the reaction was performed without preactivation or using *o*-nitrobenzenesulfonyl chloride. A 3−5 min preactivation precludes that possibility by increasing the population of the intermediate **V** in the reaction mixture.

The product as well as byproducts Oxyma (**II**) and 2-nitrobenzenesulfonic acid (**IV**) were recovered easily (Scheme 4). After completion of the reaction (entry 2, Table 4), the reaction mixture was diluted with ethyl acetate and washed with 5% citric acid solution (3 × 5 mL). The concentrated organic layer was directly purified by silica gel column chromatography. The product and byproducts were eluted with specific eluents. Purity of the recovered **II** and **IV** was as good as the commercial samples (Supporting Information Figures S103−S105). The recovered sulfonic acid was chlorinated by heating at 60 °C for 1.5 h in toluene with a small amount of DMF using thionyl chloride. Pure sulfonyl chloride, obtained in this way, was transformed to **I** by stirring with Oxyma in basic medium (DIPEA).

To the best of our knowledge, only one such recyclable coupling reagent has been reported, which is a hypervalent iodine(III) reagent, iodosodilactone, and it works in association with DMAP and PPh_3.[16] Dipeptide formation with this

Scheme 4. Recyclability of Coupling Reagent I



[a]Yield of the regenerated **I** from the recovered **II** and **IV** was calculated with respect to the initial amount of **I** used in the reaction.

combination of reagents usually takes 8 h under heating condition (60 °C). On the other hand, it takes only 1 h at room temperature (25 °C) by our method. Moreover, a stoichiometric amount of triphenyl phosphine oxide is generated with iodosodilactone/DMAP/PPh_3, whereas the present method does not leave any solid waste to the environment.

■ CONCLUSION

We have introduced a new and efficient coupling reagent, *o*-NosylOXY (**I**), for the synthesis of amide, hydroxamate, peptide, and ester. The present method is associated with the following important features: (1) apparently complete retention of stereochemistry, (2) applicability to both solution and solid-phase synthesis of large peptides with difficult sequences, (3) ease of preparation of the reagent, (4) works under ambient and milder conditions. A plausible mechanism is suggested, and an intermediate could be isolated and fully characterized which supports that. Most importantly, the reagent is recyclable and, therefore, cost-effective and environmentally friendly. All these features makes this reagent useful for industry and academia in the context of condensation chemistry.

■ EXPERIMENTAL SECTION

General Consideration. All reagents were purchased from commercial sources and were used without any further purification unless mentioned otherwise. *o*-Nitrobenzenesulfonyl chloride was freshly recrystallized before use. Dichloromethane was distilled and dried using the standard procedure. Melting points were uncorrected. Thin-layer chromatograms were run on glass plates coated with silica gel G for TLC, using the solvent system EtOAc/hexane. Compounds were purified by column chromatography using silica gel (60−120 mesh) with EtOAc/hexane (of specific proportion as required) as an eluent. ^{1}H NMR (400 and 600 MHz) and ^{13}C NMR (100 and 150 MHz) were recorded using $CDCl_3$ as solvent. Chemical shifts (δ) are reported in parts per million (ppm), internal reference (0.05% to 1%) tetramethylsilane. Coupling constants (J) are reported in Hz: singlet (s), doublet (d), triplet (t), doublet of doublet (dd), multiplet (m), or broad (br). High-resolution mass spectra were recorded on a Q-TOF ESI-MS instrument and a Q-TOF LC/MS system; HPLC analysis was carried out with either a C8 (5 μm, 3.5 × 150 mm) or a C18 (5 μm, 4.6 × 250 mm) reversed-phase column and a chiral column (5 μm, 2.1 × 150 mm) coupled to a UV detector. HPLC-grade solvents were used for HPLC analysis. IR spectra were recorded on a IR spectrometer; X-ray data were collected on a diffractometer equipped with a CCD area detector using Mo. Data for previously reported compounds (cited) matched well with our observed data.

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Procedure for Synthesis of Coupling Reagent Ethyl 2-Cyano-2-(2-nitrobenzenesulfonyloxyimino) Acetate (*o*-NosylOXY, I). DIPEA (0.87 mL, 5 mmol, 1 equiv) was added to a solution of Oxyma (710 mg, 5 mmol, 1 equiv) in 2 mL of DCM under nitrogen. The reaction mixture was cooled up to 0 °C and followed by dropwise addition of 2-nitrobenzenesulfonyl chloride (1108 mg, 1 mmol, 1 equiv) for 30 min. The reaction mixture was stirred for another 2 h at room temperature (25 °C). After completion of the reaction, the reaction mixture was diluted with 10 mL of DCM and washed with 5% of HCl (3 × 5 mL). Finally, the organic layer was dried by anhydrous $CaCl_2$ and recrystallized with hexane: R_f = 0.50 (EtOAc/hexane, 1:4); yield 1308 mg, 80%; colorless crystalline solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26−8.24 (d, J = 8.0 Hz, 1H), 7.95−7.90 (m, 1H), 7.89−7.84 (m, 2H), 4.45−4.40 (q, 2H), 1.39−1.36 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 148.6, 137.3, 133.3, 132.9, 132.7, 126.7, 125.5, 105.9, 65.0, 13.8; IR (KBr) 3103, 2988, 2224, 1748, 1545, 928, 742 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{11}H_{10}N_3O_7S$ 328.0239, found 328.0235.

General Procedure for the Synthesis of Ester and Amide. *o*-NosylOXY (1 equiv) was added to a solution of acid (1 equiv) and DIPEA (2.2 equiv) in 2 mL of DCM. The reaction mixture was stirred for 3−5 min for preactivation followed by the addition of alcohol or amine (1 equiv). The reaction mixture was stirred at room temperature for 2−3 h. After completion of the reaction, the reaction mixture was diluted with 50 mL of ethyl acetate; the organic phase was washed with 5% citric acid (3 × 20 mL) and 5% $NaHCO_3$ (3 × 20 mL) and dried by anhydrous Na_2SO_4. Finally, Na_2SO_4 was filtered off, and the solvent was evaporated to obtain the product which was purified by column chromatography.

General Procedure for the Synthesis of Dipeptides. To a solution of *N*-protected amino acid (1 equiv) and *o*-NosylOXY (1 equiv) in 2 mL of DCM was added DIPEA (1.1 equiv). The reaction mixture was stirred for 5 min for preactivation followed by the addition of methyl ester of the second amino acid (1.1 equiv) and DIPEA (1.1 equiv) in 1 mL of DCM. The reaction mixture was stirred at room temperature for more 2−3 h. After completion of the reaction, the reaction mixture was diluted with 50 mL of ethyl acetate, the organic phase was washed with 5% citric acid (3 × 20 mL), 5% $NaHCO_3$ (3 × 20 mL), and brine, and dried over anhydrous Na_2SO_4. Finally, Na_2SO_4 was filtered, and the solvent was evaporated. The product was purified by silica gel column chromatography.

General Procedure for the Synthesis of Hydroxamate. To a solution of acid or *N*-protected amino acid (1 equiv) and *o*-NosylOXY (1 equiv) in 2 mL of DCM was added DIPEA (1.1 equiv). The reaction mixture was stirred for 3−5 min for preactivation followed by the addition of *O*-benzylhydroxylamine (1.1 equiv) and DIPEA (1.1 equiv) in 1 mL of DCM. The reaction mixture was stirred at room temperature (25 °C) for an additional 2−3 h. After completion of the reaction, the reaction mixture was diluted with 50 mL of ethyl acetate, and the organic phase was washed with 5% citric acid (3 × 20 mL), 5% $NaHCO_3$ (3 × 20 mL), and brine and dried over Na_2SO_4 anhydrous. Finally, Na_2SO_4 was filtered, and the solvent was evaporated. The product was purified by silica gel column chromatography.

Solution-Phase Synthesis of Boc-VVIA-OMe. Boc-isoleucine (750 mg, 3.24 mmol, 1 equiv) and *o*-NosylOXY (1059 mg, 3.24 mmol, 1 equiv) were taken in a 25 mL round-bottom flask (RB), after which DIPEA (0.85 mL, 4.86 mmol, 1.5 equiv) was added and the solution kept 5 min for preactivation. In another oven-dried 50 mL RB, the methyl ester of alanine (675 mg, 4.86 mmol, 1.5 equiv) was taken in DCM, and DIPEA was added until basic pH was reached. Finally, this solution was added to the first RB and stirring continued until completion of the reaction. Then the reaction mixture was diluted with 50 mL of EtOAc, washed with 5% $NaHCO_3$ solution (2 × 5 mL), and washed with 5% citric acid solution (2 × 5 mL). Finally, the combined organic layer was dried using anhydrous Na_2SO_4. Solid product (Boc-IA-OMe) was obtained after evaporation of EtOAc by rotary vacuum evaporator.

In an oven-dried 50 mL RB, Boc-IA-OMe was taken and 70% TFA solution in DCM was added. Stirring continued up to 2.5 h. After that, TFA was evaporated by rotary evaporator, the solution was washed three times with diethyl ether, and finally a white solid (IA-OMe) was obtained.

After Boc deprotection, the resulting IA-OMe was coupled with Boc-V-OH following the above-mentioned procedure to obtain Boc-VIA-OMe. Another cycle of Boc-deprotection and coupling with Boc-V-OH, resulted in white solid Boc-VVIA-OMe, which was characterized by reversed-phase HPLC; retention time 12.8 min on a linear gradient of 20−100% CH_3CN/0.09% TFA in H_2O/0.09% TFA over 18 min, symmetry C8 analytical column; LRMS (ESI) m/z [M + H]$^+$ calcd for $C_{25}H_{47}N_4O_7$ 537.3264, found 537.3421. Yield was 1298 mg, 78% with respect to starting material Boc-isoleucine.

Solid-Phase Synthesis of NFGAILG-NH_2 and VQAAIDYING-NH_2. Specific amino acids were manually assembled on Fmoc-Rink Amide MBHA resin (loading 1.1 mmol/g) following the Fmoc-^{t}But orthogonal protection strategy. Fmoc-amino acids (3.2 equiv), *o*-NosylOXY (3 equiv), and DIPEA (5 equiv) were kept for preactivation for 5 min. Amino acid coupling was performed for 2 h. Fmoc deprotection was carried out with 25% piperidine/DMF (3 × 7 min). The peptide was cleaved from the resin using a TFA/DCM/H_2O mixture for 2 h 30 min. Purification of the peptide was performed using semipreparative HPLC using a linear gradient of 20 min (5 to 100% ACN in water with 0.09% TFA) and characterized using ESI-MS.

For NFGAILG-NH_2, we took 300 mg of Fmoc-Rink Amide resin (loading 1.1 mmol/g), after final coupling, peptide was cleaved from resin and purified by semipreparative HPLC. The purified yield of peptide was 90 mg, 40%; HPLC profile and ESI-MS spectra are included in the Supporting Information (Figures S153−S154).

For VQAAIDYING-NH_2, we took 300 mg of Fmoc-Rink Amide resin (loading 1.1 mmol/g); after final coupling, this peptide was also cleaved from the resin and purified by semipreparative HPLC. Yield of the purified peptide was 175 mg, 50%. HPLC profile and ESI-MS spectra are provided in the Supporting Information (Figures S167−S168).

Intermediate V (Scheme 3): Oxyma ester of naphthanoic acid: white solid; R_f = 0.40 (EtOAc/hexane, 1.0:9.0); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.13−8.11 (t, J = 8.0 Hz, 1H), 8.00−7.98 (d, J = 12.0, Hz, 1H), 7.97−7.90 (m, 2H), 7.64−7.61 (t, J = 6.5, Hz, 1H), 7.58−7.56 (t, J = 6.6 Hz, 1H), 4.46−4.43 (q, J = 6.0 Hz, 2H), 1.43−1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 157.1, 136.5, 133.1, 132.4, 129.9, 129.7, 129.2, 128.0, 127.4, 125.0, 122.8, 107.2, 64.7, 14.1; IR (KBr) 2924, 2853, 2224, 1715, 1646, 1593, 1541, 1398, 668, 544 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{16}H_{12}N_2NaO_4$ 319.0695, found 319.0691. CCDC-936483 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Methyl 2-(2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-phenylpropanamido)propanoate[17] *(by o-nitrobenzenesulfonyl chloride):* yield 307 mg (65%); white solid; R_f = 0.40 (EtOAc/hexane, 3.0:7.0); mp 178−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−8.07 (m, 1H), 7.94−7.91 (m, 1H), 7.77−7.72 (m, 2H), 7.55−7.52 (t, J = 12.0 Hz, 2H), 7.42−7.38 (t, J = 12.0 Hz, 2H), 7.32−7.24 (m, 4H), 7.21−7.19 (m, 1H), 6.33 (br, 1H), 5.39 (br, 1H), 4.52−4.43 (m, 3H), 4.32−4.23 (m, 2H), 4.20−4.17 (t, J = 8.0 Hz, 1H), 3.52 (s, 3H), 3.12−3.05 (m, 1H), 1.50−1.48 (d, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 172.1, 170.7, 156.1, 143.9, 141.4, 136.4, 133.7, 132.9, 130.6, 129.5, 128.5, 127.8, 127.8, 127.2, 125.7, 120.1, 67.2, 56.1, 52.2, 48.3, 47.2, 19.7, 18.3; IR (KBr) 3304, 1738, 1690, 1652, 1534, 1262, 698 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{28}H_{29}N_2O_5$ 473.2076, found 473.2079.

(L) Methyl 2-(2-nitrophenylsulfonamido)propanoate (by o-nitrobenzenesulfonyl chloride).[18] pale yellow solid; R_f = 0.50 (EtOAc/hexane, 3.0:7.0); mp 68−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29−8.27 (m, 1H), 8.07−8.05 (m, 1H), 7.92−7.90 (m, 1H), 7.74−7.71 (m, 1H), 6.18 (br, 1H), 4.23−4.19 (m, 1H), 3.50 (s, 3H), 1.50−1.48 (d, J = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.1, 147.9, 134.4, 133.8, 133.0, 130.6, 125.7, 52.7, 48.8, 16.7; IR (KBr) 3330, 2921, 1746, 1691, 1536, 1261, 1184, 741 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{10}H_{12}N_2NaO_6S$ 311.0314, found 311.0317.

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N-Benzyl-2-nitrobenzenesulfonamide (byproduct of the reaction without preactivation): pale yellow solid; R_f = 0.52 (EtOAc/hexane, 3.0:7.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−7.98 (m, 1H), 7.83−7.81 (m, 1H), 7.70−7.63 (m, 2H), 7.31−7.22 (m, 5H), 5.77 (br, 1H), 4.33−4.32 (d, J = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 135.8, 134.1, 133.6, 132.9, 131.1, 128.8, 128.0, 125.4, 48.0; IR (KBr) 3340, 2961, 1691, 1535, 1221, 1182, 933, 742 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{13}H_{12}N_2NaO_4S$ 315.0415, found 315.0420.

N-Benzylbenzamide (entry 1, Table 3):[19] yield 186 mg (88%); white solid; R_f = 0.50 (EtOAc/hexane, 2.0:8.0); mp 102−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78−7.76 (m, 2H), 7.42−7.37 (m, 4H), 7.36−7.28 (m, 4H), 4.63−4.62 (d, J = 4.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 138.4, 134.4, 131.6, 128.8, 128.6, 127.9, 127.5, 127.1, 44.1; IR (KBr) 3290, 2924, 1637, 1551, 765, 565 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{14}H_{14}NO$ 212.1075, found 212.1073.

N-Benzyl-2-phenylacetamide (entry 2, Table 3):[19] yield 205 mg (91%); white solid; R_f = 0.51 (EtOAc/hexane, 2.0:8.0); mp 76−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.27 (m, 5H), 7.24−7.16 (m, 5H), 5.76 (br, 1H), 4.42 (s, 2H), 3.62 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 138.3, 135.0, 129.4, 129.0, 128.7, 127.5, 127.4, 127.3, 43.7, 43.6; IR (KBr) 3289, 2925, 1638, 1552, 784, 634, 566 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{15}H_{16}NO$ 226.1232, found 226.1231.

N-(4-Methoxyphenyl)-2-phenylacetamide (entry 3, Table 3): yield 198 mg (82%); pale yellowish solid; R_f = 0.40 (EtOAc/hexane, 3.0:7.0); mp 121−123 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39−7.37 (m, 2H), 7.35−7.29 (m, 5H), 7.12 (br, 1H), 6.81−6.79 (d, J = 12.0 Hz, 2H), 3.75 (s, 3H), 3.70 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.3 156.7, 134.7, 130.8, 129.7, 129.3, 127.7, 122.0, 114.2, 55.6, 44.8; IR (KBr) 3330, 2930, 2832, 1751, 1519, 1262, 1188, 1016, 544 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{15}H_{16}NO_2$ 242.1181, found 242.1183.

2-N-Diphenylacetamide (entry 4, Table 3):[20] yield 181 mg (86%); white solid; R_f = 0.40 (EtOAc/hexane, 2.0:8.0); mp 115−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.36 (m, 5H), 7.35−7.06 (m, 5H), 3.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 137.9, 134.7, 129.5, 129.1, 128.9, 127.5, 124.5, 120.2, 44.6; IR (KBr) 3285, 2967, 1657, 1601, 865, 543 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{14}H_{14}NO$ 212.1075, found 212.1071.

Benzyl 2-oxo-2-(piperidin-1-yl) ethyl carbamate (entry 5, Table 3):[21] yield 265 mg (89%); white solid; R_f = 0.30 (EtOAc/hexane, 4.0:6.0); mp 113−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.28 (m, 5H), 5.84 (br, 1H), 5.09 (s, 2H), 3.98−3.97 (d, J = 4.0 Hz, 2H), 3.54−3.52 (t, J = 5.2 Hz, 2H), 3.29−3.27 (t, J = 5.2 Hz, 2H), 1.70−1.68 (d, J = 4.0 Hz, 2H), 1.63−1.61 (d, J = 4.8 Hz, 2H), 1.54−1.52 (d, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 156.3, 136.6, 128.5, 128.1, 128.0, 66.8, 45.4, 43.1, 42.6, 34.0, 26.2, 25.7, 25.4, 25.0, 24.3; IR (KBr) 3293, 2936, 1707, 1641, 763, 541 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{15}H_{20}N_2NaO_3$ 299.1372, found 299.1368.

(9H-Fluoren-9-yl)methyl (1-(tert-butylamino)-1-oxopropan-2-yl) carbamate (entry 6, Table 3): yield 296 mg (81%); yellowish solid; R_f = 0.40 (EtOAc/hexane, 3.0:7.0); $[\alpha]^{25}_D$ = +4.07 ($CHCl_3$, c = 0.54); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76−7.75 (d, J = 12.0 Hz, 2H), 7.59−7.57 (d, J = 12.0 Hz, 2H), 7.41−7.38 (m, 2H), 7.32−7.29 (m, 2H), 4.43−4.37 (m, 3H), 4.24−4.19 (t, J = 6.0 Hz, 1H), 4.13 (br, 1H), 1.36−1.35 (d, J = 6.0 Hz, 3H), 1.34 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 156.1, 144.0, 141.5, 127.9, 127.2, 125.2, 120.1, 67.2 51.5, 47.3, 28.8, 19.1; IR (KBr) 3330, 3231, 2984, 1754, 1243, 752, 542 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{22}H_{27}N_2O_3$ 367.2022, found 367.2025.

L-Methyl 2-(2-(((((9H-fluoren-9-yl)methoxy) carbonyl)amino)-propanamido)-2-methylpropanoate (entry 7, Table 3): yield 328 mg (80%); white solid; R_f = 0.50 (EtOAc/hexane, 3.0:7.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.75 (d, J = 12.0 Hz, 2H), 7.62−7.58 (m, 2H), 7.42−7.38 (t, J = 12.0 Hz, 2H), 7.32−7.29 (t, J = 12.0 Hz, 2H), 5.42 (br, 1H), 4.43−4.37 (m, 2H), 4.24−4.21 (t, J = 8.0 Hz, 1H), 4.16−4.10 (m, 1H), 3.76 (s, 3H), 1.44−1.42 (d, J = 12.0 Hz, 3H), 1.25 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 155.8, 144.1, 141.5, 127.9, 127.2, 125.2, 124.9, 120.2, 76.9, 67.2, 52.7, 50.5, 49.8, 47.3, 29.7, 18.9; IR (KBr) 3341, 1722, 1654, 1650, 1231, 664 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{23}H_{27}N_2O_5$ 411.1920, found 411.1922.

Methyl 2-(2-(((9H-fluoren-9-yl) methoxy)carbonyl)acetamido)-acetate (entry 8, Table 3): yield 321 mg (91%); white solid; R_f = 0.31 (EtOAc/hexane, 4.0:6.0); mp 162−163 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.74 (d, J= 8.0 Hz, 2H), 7.58−7.56 (d, J = 8.0 Hz, 2H), 7.40−7.37 (t, J= 8.0 Hz, 2H), 7.31−7.27 (t, J = 8.0 Hz, 2H), 6.80 (br, 1H), 5.73 (br, 1H), 4.43−4.41 (d, J = 6.8 Hz, 2H), 4.22−4.19 (t, J = 7.2 Hz, 1H), 4.04−4.03 (d, J = 8.0 Hz, 2H), 3.92−3.91 (d, J = 6.8 Hz, 2H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 169.7, 156.8, 143.7, 141.2, 128.6, 128.5, 128.3, 127.1, 67.1, 47.0, 44.2, 41.2, 33.8; IR (KBr) 3316, 2931, 1734, 1692, 1654, 865, 523 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{20}H_{19}NNaO_5$ 376.1161, found 376.1165.

L,L-Methyl 2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-4-methyl-pentanamido)propanoate (entry 9, Table 3). yield 390 mg (89%); white solid; R_f = 0.50 (EtOAc/hexane, 3.0:7.0); mp 161−163 °C; $[\alpha]^{25}_D$ = −16.5 ($CHCl_3$, c = 0.35); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.74 (d, J = 8.0 Hz, 2H), 7.59−7.57 (d, J = 8.0 Hz, 2H), 7.41−7.37 (t, J = 7.2 Hz, 2H), 7.32−7.28 (t, J = 7.2 Hz, 2H), 6.62 (br, 1H), 5.36−5.34 (d, J = 8.0 Hz, 1H), 4.58−4.52 (m, 1H), 4.41−4.35 (m, 1H), 4.22−4.19 (t, J = 6.4 Hz, 3H), 3.73 (s, 3H), 1.81−1.74 (m, 1H), 1.65−1.63 (m, 2H), 1.40−1.38 (d, J = 6.8 Hz, 3H), 1.01−0.98 (d, J = 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 163.1, 156.6, 143.8, 141.1, 129.3, 128.6, 127.5, 126.9, 124.9, 66.6, 57.4, 52.2, 46.9, 38.2, 38.3, 28.1, 18.0; IR (KBr) 3307, 2925, 1754, 1694, 1654, 879, 534 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{25}H_{31}N_2O_5$ 439.2233, found 439.2235.

L,L-Methyl 2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-methyl-butanamido)propanoate (entry 10, Table 3):[22] yield 369 mg (87%); white solid; R_f = 0.50 (EtOAc/hexane, 3.0:7.0); mp 204−205 °C; $[\alpha]^{25}_D$ = −14.5 ($CHCl_3$, c = 0.40); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.75 (d, J = 8.0 Hz, 2H), 7.60−7.58 (d, J = 8.0 Hz, 2H), 7.41−7.37 (t, J = 8.0 Hz, 2H), 7.31−7.28 (t, J = 8.0 Hz, 2H), 6.54−6.52 (d, J = 8.0 Hz, 1H), 5.54−5.52 (d, J = 8.0 Hz, 1H), 4.60−4.58 (d, J = 8.0 Hz, 2H), 4.44−4.35 (m, 1H), 4.23−4.21(d, J = 8.0 Hz, 1H) 4.04−4.00 (t, J = 7.0 Hz, 1H), 3.73 (s, 3H), 2.11−2.08 (m, 1H), 1.41−1.39 (d, J = 8.0 Hz, 3H), 0.98−0.96 (d, J = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 171.2, 156.6, 144.0, 141.4, 127.8, 127.2, 125.2, 120.1, 67.2, 60.4, 52.6, 48.2, 47.3, 31.9, 29.8, 19.2, 18.2; IR (KBr) 3296, 2953, 1745, 1692, 1650, 765, 599 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{24}H_{28}N_2NaO_5$ 447.1896, found 447.1901.

L-Methyl 2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)-3-phenyl-propanamido)acetate (entry 11, Table 3): yield 412 mg (93%); white solid; R_f = 0.52 (EtOAc/hexane, 3.0:7.0); mp 175−178 °C; $[\alpha]^{25}_D$ = −6.5 ($CHCl_3$, c = 0.60); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77−7.75 (d, J = 8.0 Hz, 4H), 7.54−7.50 (t, J = 8.0 Hz, 2H), 7.42−7.38 (t, J = 8.0 Hz, 2H), 7.32−7.28 (m, 5H), 6.31 (br, 1H), 5.33 (br, 1H), 4.45−4.40 (t, J = 8.0 Hz, 2H), 4.40−4.32 (d, J = 8.0 Hz, 1H), 4.20−4.16 (t, J = 7.2 Hz, 1H), 4.00−3.99 (d, J = 4.0 Hz, 2H) 3.72 (s, 3H); 3.10−3.00 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 170.0, 156.2, 143.8, 141.4, 136.5, 129.4, 128.8, 128.5, 127.8, 127.7, 127.3, 127.2, 125.1, 120.1, 67.2, 56.1, 52.5, 47.2, 41.3, 38.5; IR (KBr) 3300, 1749, 1692, 1651, 1539, 1260, 757; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{27}H_{26}NO_5$ 444.1811, found 444.1809.

L-Methyl 2-(2-(((9H-fluoren-9-yl)methoxy)carbonyl)propan-amido)acetate (entry 12, Table 3:). yield 319 mg (87%); white solid; R_f = 0.40 (EtOAc/hexane, 4.0:6.0); mp 157−159 °C; $[\alpha]^{25}_D$ = −12.4 ($CHCl_3$, c = 0.60); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75−7.73 (d, J = 8.0 Hz, 2H), 7.56−7.55 (d, J = 8.0 Hz, 2H), 7.39−7.35 (t, J = 8.0 Hz, 2H), 7.30−7.27 (t, J = 8.0 Hz, 2H), 6.63 (br, 1H), 5.54 (br, 1H), 4.39−4.38 (t, J = 4.0 Hz, 2H), 4.31−4.30 (t, J = 4.0 Hz, 1H), 4.20−4.17 (d, J = 4.0 Hz, 1H), 4.01−3.99 (d, J = 4.0 Hz, 2H), 3.71 (s, 3H), 1.40−1.38 (d, J = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.9, 170.2, 156.2, 143.9, 141.4, 127.8, 127.2, 125.2, 120.1, 67.2, 52.5, 50.5, 47.2, 41.3, 18.7; IR (KBr) 3294, 1731, 1693, 1648, 1551, 1265, 758 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{21}H_{23}N_2O_5$ 383.1607, found 383.1609.

DL-Methyl 2-(2-(benzyloxycarbonyl)-3-phenyl propanamido)-propanoate (entry 13, Table 3):[23] yield 345 mg (90%); white

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solid; R_f = 0.51 (EtOAc/hexane, 3.0:7.0); mp 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.30 (m, 4H), 7.29−7.26 (m, 4H), 7.23−7.17 (m, 2H), 6.60 (br, 1H), 5.53 (br, 1H), 5.05 (s, 2H), 4.53−4.51 (d, J = 8.0 Hz, 1H), 4.47−4.45 (d, J = 8.0 Hz, 1H), 3.67 (s, 3H), 3.07−3.05 (d, J = 8.0 Hz, 2H), 1.32−1.30 (d, J = 8.0 Hz, 3H), 1.21−1.19 (d, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 172.9, 170.9, 170.7, 156.1, 136.6, 136.3, 129.3, 128.4, 128.1, 127.9, 126.9, 66.9, 56.1, 52.4, 38.9, 38.6, 17.8 ppm; IR (KBr) 3305, 1737, 1690, 1652, 1537, 1262, 698 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{21}H_{24}N_2NaO_5$ 407.1583, found 407.1588.

L-Methyl 2-(2-(benzyloxycarbonyl)-3-phenylpropanamido)-propanoate (entry 14, Table 3):[23] yield 349 mg (91%); white solid; R_f = 0.51 (EtOAc/hexane, 3.0:7.0); mp 120−122 °C; $[\alpha]^{25}_D$ = −12.1 ($CHCl_3$, c = 0.32); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.31 (m, 4H), 7.30−7.24 (m, 4H), 7.22−7.17 (m, 2H), 6.47 (br, 1H), 5.42 (br, 1H), 5.07 (s, 2H), 4.51−4.52 (d, J = 4.0 Hz, 1H), 4.48−4.46 (d, J = 8.0 Hz, 1H), 3.70 (s, 3H), 3.07−3.05 (d, J = 8.0 Hz, 2H), 1.32−1.31 (d, J = 4.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 170.7, 156.2, 136.4, 129.5, 128.8, 128.7, 128.6, 128.3, 128.2, 127.2, 67.2, 56.2, 52.6, 49.3, 48.1, 38.7, 18.4; IR (KBr) 3305, 1737, 1690, 1652, 1537, 1262, 698 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{21}H_{24}N_2NaO_5$ 407.1583, found 407.1587.

L,L-Methyl 2-(2-(benzyloxycarbonyl)-4-(methylthio)butanamido)-propanoate (entry 15, Table 3): yield 327 mg (89%); white solid; R_f = 0.40 (EtOAc/hexane, 3.0:7.0); mp 107−110 °C; $[\alpha]^{25}_D$ = +6.8 ($CHCl_3$, c = 0.70); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.32 (m, 3H), 7.30−7.27 (m, 2H), 6.69 (br, 1H), 5.55 (br, 1H), 5.08 (s, 2H), 4.55−4.52 (t, J = 8.0 Hz, 1H), 4.39−4.37 (t, J = 8.0 Hz, 1H), 3.71 (s, 3H), 2.59−2.56 (t, J = 8.0 Hz, 2H), 2.08 (s, 3H), 2.00−1.94 (q, J = 8.0 Hz, 2H), 1.38−1.37 (d, J = 4.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 170.8, 156.1, 136.3, 128.7, 128.4, 128.3, 67.3, 54.0, 52.7, 48.3, 31.9, 30.0, 18.3, 15.4 ppm; IR (KBr) 3299, 1735, 1688, 1647, 1538, 1265, 697 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{17}H_{25}N_2O_5S$ 369.1484, found 369.1489.

L-Methyl 2-(2-(benzyloxycarbonyl)-2-methylpropanamido)-propanoate (entry 16, Table 3):[22] yield 260 mg (81%); yellowish solid; R_f = 0.50 (EtOAc/hexane, 2.0:8.0); mp 67−70 °C; $[\alpha]^{25}_D$ = −1.8 ($CHCl_3$, c = 0.70); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28−7.22 (m, 3H), 7.21−7.15 (m, 2H), 6.89 (br, 1H), 5.82−5.76 (t, J = 8.0 Hz, 1H), 4.98 (s, 2H), 4.43 (br, 1H), 3.58 (s, 3H), 1.32 (s, 6H), 1.17−1.14 (d, J = 4.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.2, 173.5, 155.1, 136.4, 128.5, 128.1, 128.0, 66.6, 56.8, 52.4, 48.2, 25.1, 25.1, 18.0; IR (KBr) 3316, 1734, 1692, 1654, 1234, 674 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{23}N_2O_5$ 323.1607, found 323.1610.

L-Methyl 2-(2-(benzyloxycarbonyl)-2-methylpropanamido)-4-methylpentanoate (entry 17, Table 3):[22] yield 283 mg (78%); white solid; R_f = 0.50 (EtOAc/hexane, 2.0:8.0); mp 77−80 °C; $[\alpha]^{25}_D$ = −1.5 ($CHCl_3$, c = 1.64); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35−7.32 (m, 3H), 7.31−7.26 (m, 2H), 6.70 (br, 1H), 5.31 (br, 1H), 5.09 (s, 2H), 4.60−4.58 (t, J = 4.0 Hz, 1H), 3.71 (s, 3H), 1.65−1.61 (m, 3H), 1.50 (s, 3H), 1.49 (s, 3H), 0.95−0.92 (d, J = 4.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.3, 173.6, 155.3, 136.4, 128.7, 128.6, 128.9, 66.9, 57.2, 52.39, 51.9, 41.6, 25.9, 25.2, 25.0, 22.9, 22.0; IR (KBr) 3346, 1723, 1653, 1653, 1235, 664 cm^1; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{29}N_2O_5$ 365.2076, found 365.2080.

L,L-2-[2-(2-Benzyloxycarbonylaminoacetylamino)-3-phenylpropionylamino]-3-methylbutyric acid methyl ester (entry 18, Table 3):[23] yield 426 mg (91%); white solid; R_f = 0.31 (EtOAc/hexane, 3.0:7.0); mp 101 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 7.23−7.11 (m, 5H), 5.88 (br, 1H), 5.11 (s, 2H), 4.78 (br, 1H), 443−4.40 (m, 2H), 3.88−3.84 (m, 2H), 3.60 (s, 3H), 304−299 (m, 2H), 2.06−2.03 (m, 1H), 0.87−0.84 (d, J = 8.0 Hz, 3H), 0.82−0.79 (d, J = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9, 171.4, 169.6, 156.7, 136.5, 136.4, 129.4, 129.0, 128.7, 128.6, 128.5, 128.1, 128.0, 126.8, 67.0, 57.5, 54.5, 52.0, 44.2, 38.5, 31.1, 18.8, 17.9; IR (KBr) 3406, 1728, 1677, 1651, 1646, 763, 543 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{25}H_{32}N_3O_6$ 470.2291, found 470.2294.

N-(Benzyloxy)benzamide (entry 1, Table 4):[24] yield 208 mg (92%), yellowish solid; R_f = 0.50 (EtOAc/hexane, 2.0:8.0); mp 107−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−8.10 (m, 2H), 7.69−7.51 (m, 2H), 7.49−7.35 (m, 6H), 5.02 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 133.8, 132.1, 130.3, 129.7, 129.4, 128.8, 128.7, 128.6, 128.5, 127.3, 78.5; IR (KBr) 2963, 1626, 1522, 1145, 1001, 747, 638 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{14}H_{14}NO_2$ 228.1025, found 228.1023.

N-(Benzyloxy)-2-naphthamide (entry 2, Table 4): yield 249 mg (90%); white solid; R_f = 0.50 (EtOAc/hexane, 2.0:8.0); mp 126−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, br), 8.16 (s, 1H), 7.82−7.79 (d, J = 12.0 Hz, 2H), 7.70−7.68 (m, 1H), 7.53−7.46 (m, 2H), 7.43−7.42 (m, 3H), 7.38−7.34 (m, 3H), 5.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 135.2, 135.0, 132.8, 129.6, 129.3, 129.1, 128.9, 128.2, 128.0, 127.1, 123.7, 78.4; IR (KBr) 3208, 2920, 1647, 1501, 1123, 908, 752, 699, 533, 505 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{16}NO_2$ 278.1181, found 278.1185.

N-(Benzyloxy)-3-(1H-indol-3-yl)propanamide (entry 3, Table 4):[25] yield 261 mg (89%); white solid; R_f = 0.50 (EtOAc/hexane, 2.0:8.0); mp 145−147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57−7.55 (d, J = 8.0 Hz, 1H), 7.37−7.35 (d, J = 8.0 Hz, 1H), 7.34−7.27 (m, 3H), 7.18−7.16 (m, 3H), 7.09−7.05 (m, 1H), 6.98 (s, 1H), 4.70 (s, 2H), 3.10−3.06 (t, J = 8.0 Hz, 2H), 2.42−2.38 (t, J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 136.4, 135.1, 129.0, 128.3, 128.1, 126.8, 122.0, 121.3, 118.5, 118.1, 113.3, 111.2, 76.9, 33.7, 21.0; IR (KBr) 3402, 2922, 1656, 1502, 1145, 1001, 743, 698, 616, 516 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{19}N_2O_2$ 295.1447, found 295.1443.

(9H-Fluoren-9-yl)methyl 2-(benzyloxyamino)-2-oxoethyl carbamate (entry 4, Table 4): yield 366 mg (91%); white solid; R_f = 0.40 (EtOAc/hexane, 4.0:6.0); mp 114−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (br, 1H), 7.76−7.73 (d, J = 12.0 Hz, 2H), 7.41−7.38 (m, 2H), 7.36−7.27 (m, 4H), 7.15−7.11 (m, 5H), 5.58 (br, 1H), 4.85 (s, 2H), 4.26−4.24 (d, J = 8.0 Hz, 2H), 4.07−4.06 (d, J = 4.0 Hz, 2H), 3.70−3.68 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 156.9, 143.8, 141.4, 129.4, 128.9, 128.7, 127.9, 127.2, 125.2, 120.1, 78.5, 67.5, 47.2, 42.6; IR (KBr) 3334, 2912, 1702, 1674, 1540, 1272, 1167, 756, 698, 534 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{24}H_{23}N_2O_4$ 403.1658, found 403.1654.

(9H-Fluoren-9-yl)methyl 1-(benzyloxyamino)-1-oxopropan-2-yl carbamate (entry 5, Table 4):[26] yield 366 mg (88%); white solid; R_f = 0.50 (EtOAc/hexane, 4.0:6.0); mp 142−144 °C; $[\alpha]^{25}_D$ = −13.4 ($CHCl_3$, c = 0.10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (br, 1H), 7.75−7.73 (d, J = 8.0 Hz, 2H), 7.54−7.53 (d, J = 4.0 Hz, 2H), 7.38−7.32 (m, 4H), 7.31−7.25 (m, 5H), 5.51 (br, 1H), 4.86 (s, 2H, 2H), 4.30 (d, J = 4.0 Hz, 2H), 4.14−4.12 (m, 2H), 1.25 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 156.2, 143.7, 141.4, 135.1, 129.3, 128.9, 128.7, 127.9, 127.2, 125.2, 120.1, 78.3, 67.3, 48.2, 47.1, 18.0; IR (KBr) 3294, 2923, 1690, 1664, 1537, 1260, 755, 739, 521 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{25}H_{25}N_2O_4$ 417.1814, found 417.1811.

(9H-Fluoren-9-yl)methyl 1-(benzyloxyamino)-4-methyl-1-oxopentan-2-yl carbamate (Entry 6, Table.4): yield 385 mg (84%); white solid; R_f = 0.50 (EtOAc/hexane, 3.0:7.0); mp 157−160 °C; $[\alpha]^{25}_D$ = −12.4 ($CHCl_3$, c = 0.41); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (br, 1H), 7.73−7.71 (d, J = 8.0 Hz, 2H), 7.57−7.49 (m, 4H), 7.35−7.25 (m, 7H), 5.59 (d, J = 8.0 Hz, 1H), 4.85 (s, 2H), 4.29−4.27 (d, J = 8.0 Hz, 2H), 4.23−4.20 (t, J = 8.0 Hz, 1H), 4.14−4.12 (t, J = 8.0 Hz, 1H), 1.57−1.54 (m, 2H), 0.92−0.91 (d, J = 4.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 156.4, 143.7, 141.3, 135.1, 129.3, 128.7, 128.5, 127.4, 127.1, 125.1, 120.0, 78.2, 67.3, 50.9, 47.0, 41.3, 24.7, 22.6, 22.4; IR (KBr) 3311, 2957, 1688, 1666, 1535, 1248, 1040, 765, 532, 458 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{28}H_{31}N_2O_4$ 459.2284, found 459.2279.

(9H-Fluoren-9-yl)methyl 1-(benzyloxyamino)-3-methyl-1-oxobutan-2-yl carbamate (entry 7, Table 4): yield 364 mg (82%); white solid; R_f = 0.40 (EtOAc/hexane, 3.0:7.0); mp 205−208 °C; $[\alpha]^{25}_D$ = −18.7 ($CHCl_3$, c = 0.50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.54 (br, 1H), 7.73−7.71 (d, J = 8.0 Hz, 2H), 7.53−7.51 (m, 2H), 7.36−7.35 (m, 3H), 7.27−7.24 (m, 6H), 5.72−5.70 (d, J = 8.0 Hz, 1H), 4.84 (s, 2H), 4.30−4.28 (d, J = 8.0 Hz, 2H), 4.22−4.19 (d, J = 4.0 Hz, 1H), 2.04−2.01 (m, 1H), 0.91 (d, J = 4.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.0, 156.7, 143.8, 141.4, 135.1, 129.4, 128.9, 128.6, 127.3, 127.2, 125.3, 120.1, 78.5, 67.4, 58.3, 47.2, 31.1, 19.2, 18.5; IR (KBr)

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3281, 2961, 1698, 1657, 1544, 1294, 1251, 748, 742, 541 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{27}H_{29}N_2O_4$ 445.2127, found 445.2131.

(9H-Fluoren-9-yl)methyl 1-(benzyloxyamino)-4-(methylthio)-1-oxobutan-2-yl carbamate (entry 8, Table 4): yield 385 mg (81%); white solid; R_f = 0.50 (EtOAc/hexane, 3.0:7.0); mp 171−174 °C; $[\alpha]^{25}_D$ = −15.3 ($CHCl_3$, c = 0.37); ^1H NMR (600 MHz, $CDCl_3$) δ 9.05 (br, 1H), 7.76−7.74 (d, J = 8.0 Hz, 2H), 7.54−7.51 (m, 2H), 7.37−7.35 (m, 3H), 7.28−7.25 (m, 6H), 5.52 (br, 1H), 4.89 (s, 2H), 4.30−4.28 (d, J = 8.0 Hz, 2H), 4.22−4.19 (m, 2H), 2.59−2.56 (q, J = 4.0 Hz, 2H), 2.09 (s, 3H), 2.04−2.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 156.4, 143.7, 141.4, 135.1, 129.4, 128.9, 128.6, 127.3, 127.2, 125.3, 120.1, 78.5, 67.4, 51.3, 47.2, 31.6, 30.0, 15.5; IR (KBr) 3281, 2961, 1698, 1657, 1544, 1294, 1251, 748, 742, 541 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{27}H_{29}N_2O_4S$ 477.1848, found 477.1852.

Phenyl 2-phenylacetate (entry 1, Table 6):[27] yield 184 mg (87%); yellowish oil; R_f = 0.51 (EtOAc/hexane, 1.0:9.0); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.30 (m, 7H), 7.22−7.18 (m, 1H), 7.05−7.04 (m, 2H), 3.85 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 151.2, 134.0, 129.8, 129.7, 129.1, 127.7, 126.2, 121.8, 41.7; IR (KBr) 2924, 2853, 1759, 1593, 1398, 1261, 1088, 1016, 696; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{13}O_2$ 213.091, found 213.0911.

4-Methoxyphenyl 2-phenylacetate (entry 2, Table 6): yield 198 mg (82%); clear oil; R_f = 0.50 (EtOAc/hexane, 1.0:9.0); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37−7.35 (m, 5H), 6.97−6.95 (d, J = 8.0 Hz, 2H), 6.86−6.84 (d, J = 8.0 Hz, 2H), 3.83 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 157.5, 144.6, 133.7, 129.5, 128.9, 127.5, 122.4, 114.6, 55.7, 41.5; IR (KBr) 2930, 2837, 1754, 1509, 1267, 1188, 1016, 544 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{15}H_{14}NaO_3$ 265.0835, found 265.0832.

4-Nitrophenyl 2-phenylacetate (entry 3, Table 6): yield 231 mg (90%); clear oil; R_f = 0.50 (EtOAc/hexane, 1.0:9.0); ^1H NMR(400 MHz, $CDCl_3$) δ 8.26−8.23 (d, J = 12.0 Hz, 2H), 7.39−7.37 (m, 5H), 7.26−7.24 (d, J = 8.0 Hz, 2H), 3.90 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.3, 155.6, 145.5, 130.5, 129.5, 128.8, 127.9, 125.5, 122.5, 41.5; IR (KBr) 2924, 2851, 1764, 1593, 1524, 1347, 1216, 1114 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{14}H_{11}NNaO_4$ 280.0586, found 280.0583.

Pentafluorophenyl 2-phenylacetate (entry 4, Table 6):[28] yield 245 mg (81%); clear oil; R_f = 0.51 (EtOAc/hexane, 1.0:9.0); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.38 (m, 2H), 7.36−7.32 (m, 3H), 3.96 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 132.3, 129.4, 129.2, 129.0, 128.8, 128.0, 127.7, 40.1; IR (KBr) 3055, 2929, 1776, 1740, 1456, 1220, 1094, 1003, 732, 696, 557 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{14}H_7F_5NaO_2$ 325.0258, found 325.0256.

Benzyl 2-phenylacetate (entry 5, Table 6):[29] yield 229 mg (92%); colorless oil; R_f = 0.60 (EtOAc/hexane, 1.0:9.0); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.31 (m, 5H), 7.28−7.26 (m, 5H), 5.13 (s, 2H), 3.67 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 135.9, 134.0, 129.3, 128.6, 128.6, 128.2, 128.1, 127.2, 66.6, 41.3; IR (KBr) 3032, 1737, 1497, 1455, 1259, 1146, 725, 491 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{15}H_{14}NaO_2$ 249.0886, found 249.0889.

tert-Butyl 2-phenylacetate (entry 6, Table 6):[30] yield 161 mg (84%); clear oil; R_f = 0.50 (EtOAc/hexane, 1.0:9.0); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.22 (m, 5H), 3.51 (s, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 134.7, 129.2, 128.5, 126.8, 80.7, 42.6, 28.0; IR (KBr) 3230, 2989, 1754, 1243, 752, 543 cm^{-1}; HRMS (ESI) m/z[M + Na]$^+$ calcd for $C_{12}H_{16}NaO_2$ 215.1048, found 215.1051.

Isopropyl 2-phenylacetate (entry 7, Table 6): yield 158 mg (89%); clear oil; R_f = 0.51 (EtOAc/hexane, 1.0:9.0); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.29 (m, 3H), 7.28−7.26 (m, 2H), 5.03−4.97 (m, 1H), 3.57 (s, 2H), 1.22 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 134.4, 129.3, 128.6, 127.0, 68.2, 41.8, 21.8; IR (KBr) 2934, 2827, 1754, 1522, 1436, 1266, 1126, 563 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{11}H_{14}NaO_2$ 201.0891, found 201.0894.

Benzyl benzoate (entry 8, Table 6):[27] yield 180 mg (85%); colorless oil; R_f = 0.50 (EtOAc/hexane, 2.0:8.0); ^1H NMR (400 MHz, $CDCl_3$) δ 8.09−8.06 (d, J = 12 Hz, 2H), 7.57−7.53 (t, 1H), 7.45−7.42 (m, 3H), 7.40−7.33 (m, 4H), 5.39 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 136.2, 133.1, 130.3, 129.8, 128.7, 128.5, 128.4, 128.3, 66.8; IR (KBr) 2853, 1749, 1543, 1352, 1273, 1043, 654, 544 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{14}H_{12}NaO_2$ 235.0735, found 235.0738.

Benzyl butyrate (entry 9, Table 6):[31] yield 162 mg (91%); oily; R_f = 0.50 (EtOAc/hexane, 0.5:9.5); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.34 (m, 1H), 7.31−7.30 (m, 4H), 5.10 (s, 2H), 2.34−2.31 (t, J = 8.0 Hz, 2H), 1.69−1.64 (q, 2H), 0.95−0.92 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 136.3, 128.6, 128.2, 66.1, 36.2, 18.5, 13.7; IR (KBr) 2928, 1738, 1754, 1381, 1253, 1171, 697 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{11}H_{14}NaO_2$ 201.0891, found 201.0889.

Naphthalen-2-yl 4-nitrobenzoate (entry 10, Table 6): yield 263 mg (90%); white solid; R_f = 0.51 (EtOAc/hexane, 1.0:9.0); mp 167−170 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 8.65−8.54 (d, J = 8.0 Hz, 1H), 8.50−8.48 (d, J = 8.0 Hz, 1H), 7.92−7.84 (m, 3H), 7.75−7.70 (m, 2H), 7.52−7.49 (m, 2H) 7.37−7.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 151.0, 148.3, 135.1, 133.9, 131.8, 131.4, 129.9, 128.0, 127.9, 127.8, 127.0, 126.8, 126.2, 126.0, 123.9, 120.8, 118.7; IR (KBr) 2922, 2852, 1724, 1593, 1424, 1347, 1299, 1096 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{17}H_{11}NNaO_4$ 316.0586, found 316.0583.

(9H-Fluoren-9-yl)methyl 4-bromobenzoate (entry 11, Table 6):[32] yield 336 mg (89%); white crystalline solid; R_f = 0.50 (EtOAc/hexane, 1.0:9.0); mp 98−102 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91−7.89 (d, J = 8.0 Hz, 2H), 7.78−7.76 (d, J = 8.0 Hz, 2H), 7.61−7.59 (m, 4H), 7.48−7.42 (t, J = 8.0 Hz, 2H), 7.32−7.28 (t, J = 8.0 Hz, 2H), 4.61−4.59 (d, J = 8.0 Hz, 2H), 4.37−4.35 (t, J = 8.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.9, 143.8, 141.5, 132.1, 131.3, 129.2, 128.4, 128.0, 127.3, 125.1, 120.3, 67.4, 47.1; IR (KBr) 3030, 2890, 1727, 1590, 1452, 1241, 1118, 1010, 751, 551 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{21}H_{15}BrNaO_2$ 401.0153, found 401.0157.

Butyl cinnamate (entry 12, Table 6): yield 186 mg (91%); clear oil; R_f = 0.50 (EtOAc/hexane, 1.0:9.0); ^1H NMR (400 MHz, $CDCl_3$) δ 7.86−7.64 (d, J = 12.0 Hz, 1H), 7.51−7.49 (m, 2H), 7.37−7.35 (m, 3H), 6.44−6.40 (d, J = 12.0 Hz, 1H), 4.20−4.17 (t, J = 8.0 Hz, 2H), 1.70−1.63 (m, 2H), 1.44−1.39 (m, 2H), 0.96−0.92 (t, J = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.2, 144.6, 134.6, 130.3, 129.0, 128.1, 118.47, 64.5, 30.9, 19.3, 13.8; IR (KBr) 2960, 2873, 1714, 1638, 1450, 1311, 1172, 980, 767, 684, 486 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{13}H_{16}NaO_2$ 227.1048, found 227.1045.

Butyl 2-naphthoate (entry 13, Table 6): yield 198 mg (87%); oily; R_f = 0.51 (EtOAc/hexane, 1.0:8.0); ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.08−8.06 (d, J = 8.0 Hz, 2H), 8.93−8.91 (d, J = 8.0 Hz, 2H), 7.84−7.81 (m, 2H), 4.39−4.36 (t, J = 4.0 Hz, 2H), 1.82−1.75 (q, 2H), 1.53−1.47 (q, 2H), 1.01−0.98 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 135.5, 132.5, 130.9, 129.3, 128.2, 127.8, 126.6, 125.3, 65.0, 30.9, 19.4, 13.8; IR (KBr) 2959, 2873, 1716, 1632, 1466, 1286, 1196, 955, 779, 474 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{15}H_{16}NaO_2$ 251.1048, found 251.1051.

4-Methoxyphenyl palmitate (entry 1, Table 7):[33] yield 311 mg (86%); white solid powder; R_f = 0.50 (EtOAc/hexane, 0.5:9.5); mp 51−52 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.98−6.95 (d, J = 12.0 Hz, 2H), 6.87−6.85 (d, J = 8.0 Hz, 2H), 3.77 (s, 3H), 2.52−2.48 (t, J = 8.0 Hz, 2H), 1.72−1.70 (m, 2H), 1.26−1.21 (m, 24H), 0.87−0.84 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 157.3, 144.5, 122.4, 114.5, 55.6, 34.5, 32.1, 29.8, 29.7, 29.6, 29.5, 29.4, 29.2, 25.1, 22.9 14.3; IR (KBr) 2916, 2849, 1746, 1552, 1509, 1463, 1213, 1033, 844 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{23}H_{38}NaO_3$ 385.2719, found 385.2716.

4-Nitrobenzyl tetradecanoate (entry 2, Table 7): yield 308 mg (92%); oily; R_f = 0.51 (EtOAc/hexane, 0.5:9.5); ^1H NMR (400 MHz, $CDCl_3$) δ 8.20−8.18 (d, J = 8.0 Hz, 2H), 7.49−7.47 (d, J = 8.0 Hz, 2H), 5.17 (s, 2H), 2.38 (t, J = 8.0 Hz, 2H), 1.64−1.60 (m, 2H), 1.26−1.21 (m, 16H), 0.85−0.82 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 147.7, 143.6, 128.4, 123.8, 64.6, 34.3, 32.0, 29.7, 29.5, 29.4, 29.3, 29.2, 25.0, 22.8, 14.2; IR (KBr) 2926, 2853, 1743, 1607, 1524, 1347, 1015, 859, 738 cm^{-1}; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{19}H_{30}NO_4$ 336.2175, found 336.2171.

Naphthalen-2-yl octanoate (entry 3, Table 7): yield 246 mg (91%); white solid; R_f = 0.50 (EtOAc/hexane, 1.0:9.0); mp 42−43 °C;

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^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.81 (m, 2H), 7.78−7.76 (d, J = 8.0 Hz, 1H), 7.53 (s, 1H), 7.46−7.43 (m, 2H), 7.22−7.19 (m, 1H), 2.61−2.57 (t, J = 8.0 Hz, 2H), 1.81−1.74 (m, 2H), 1.43−1.31 (m, 10H), 0.91−0.88 (t, J = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6, 148.6, 134.0, 131.6, 129.5, 127.9, 127.8, 126.7, 125.8, 121.4, 118.7, 34.6, 31.8, 29.3, 29.1, 25.2, 22.8, 14.2; IR (KBr) 2928, 2852, 1751, 1510, 1211, 1162, 812, 634, 483 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{18}H_{22}NaO_2$ 293.1517, found 293.1521.

4-Nitrophenyl 2-hydroxybenzoate (entry 4, Table 7):[34] yield 224 mg (82%); colorless solid; R_f = 0.50 (EtOAc/hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.53 (s, 1H), 8.25−8.23 (d, J = 8.0 Hz, 2H) 7.88−7.86 (d, J = 8.0 Hz, 1H), 7.60−7.58 (d, J = 8.0 Hz, 2H), 7.49−7.45 (t, J = 8.0 Hz, 1H), 6.99−6.97 (d, J = 8.0 Hz, 1H), 6.91−6.87 (t, J = 8.0 Hz, 1H), 5.22 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 162.0, 148.0, 142.6, 136.4, 129.9, 128.6, 124.0, 119.5, 117.9, 112.0, 65.5; IR (KBr) 3427, 2967, 2851, 1725, 1524, 1339, 1253, 754, 532 cm^{-1}; HRMS (ESI) m/z [M-H]$^-$ calcd for $C_{14}H_{10}NO_5$ 272.0559, found 272.0557.

Hexadecyl 3-(1H-indol-3-yl)propanoate (entry 5, Table 7):[35] yield 355 mg (86%); yellowish crystalline solid; R_f = 0.50 (EtOAc/hexane, 2.0:8.0); mp 60−62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (br, 1H), 7.60−7.58 (d, J = 8.0 Hz, 1H), 7.34−7.32 (d, J = 8.0 Hz, 1H), 7.20−7.16 (t, J = 8.0 Hz, 1H), 7.13−7.09 (t, J = 8.0 Hz, H), 6.98 (s, 1H), 4.07−4.04 (t, 2H), 3.11−3.07 (t, J = 8.0 Hz, 2H), 2.72−2.68 (t, J = 8.0 Hz, 2H), 1.59−1.57 (m, 2H), 1.26−1.23 (m, 26H), 0.90−0.85 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 136.5, 127.3, 122.1, 121.6, 119.4, 118.8, 115.0, 111.3, 64.8, 35.2, 32.1, 29.8, 29.7, 29.5, 29.4, 28.8, 26.1, 25.8, 22.8, 20.8, 14.3; IR (KBr) 3342, 2916, 2848, 1718, 1471, 1279, 1186, 734, 552 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{27}H_{44}NO_2$ 414.3372, found 414.3368.

Ethyl 3-(indolin-3-yl)propanoate (entry 6, Table 7):[36] yield 195 mg (90%); yellowish solid; R_f = 0.50 (EtOAc/hexane, 2.0:8.0); mp 39−41 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (br, 1H), 7.60−7.58 (d, J = 8.0 Hz, 1H), 7.30−7.28 (d, J = 8.0 Hz, 1H), 7.19−7.15 (t, J = 8.0 Hz, 1H), 7.12−7.08 (t, J = 8.0 Hz, H), 6.97 (s, 1H), 4.15−4.07 (q, 2H), 3.11−3.07 (t, J = 8 Hz, 2H), 2.72−2.68 (t, J = 8.0 Hz, 2H), 1.23−1.19 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 136.4, 127.2, 122.0, 121.7, 119.2, 118.7, 114.6, 111.3, 60.5, 35.1, 20.7, 14.2; IR (KBr) 3345, 2926, 2841, 1728, 1472, 1272, 1183, 724, 562 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{13}H_{16}NO_2$ 218.1181, found 218.1177.

(1S,2R,5S)-2-Isopropyl-5-methylcyclohexyl nicotinate (entry 7, Table 7):[35] yield 235 mg (90%); oily, R_f = 0.50 (EtOAc/hexane, 1.0:9.0); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.73−8.71 (d, J = 8.0 Hz, 1H), 8.26−8.24 (d, J = 8.0 Hz, 1H), 7.36−7.33 (t, J = 8.0 Hz, 1H), 4.96−4.89 (s, 1H), 2.10−2.05 (m, 1H), 1.91−1.87 (m, 1H), 1.72−1.67 (m, 2H), 1.56−1.49 (m, 2H), 1.12−1.06 (m, 2H), 0.93−0.88 (m, 6H), 0.76−074 (d, J = 8.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.9, 153.3, 151.0, 137.2, 126.8, 123.4, 75.7, 47.3, 41.0, 34.4, 31.6, 26.7, 23.8, 22.1, 20.9, 16.6 ppm; IR (KBr) 2957, 2870, 1719, 1591, 1289, 1121, 741 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{24}NO_2$ 262.1807, found 262.1810.

2-Octyldodecyl benzoate (entry 8, Table 7): yield 358 mg (89%); oily; R_f = 0.50 (EtOAc/hexane, 0.5:9.5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−8.01 (d, J = 8.0 Hz, 2H), 7.55−7.53 (m, 1H), 7.42−7.40 (m, 2H), 4.21−4.17 (m, 1H), 1.76−1.74 (m, 1H), 1.29−1.23 (m, 32H), 0.86−0.83 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 132.8, 130.7, 129.8, 129.4, 128.4, 128.1, 67.8, 37.6, 37.3, 32.1, 31.8, 31.6, 31.3, 31.1, 30.1, 29.8, 29.7, 29.5, 27.0, 26.8, 26.6, 22.8, 22.6, 14.3, 14.0; IR (KBr) 2925, 2854, 1723, 1466, 1272, 1133, 710 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{27}H_{46}NaO_2$ 425.3319, found 425.3314.

Methyl 2-(((9H-fluoren-9-yl)methoxy)carbonyl) propanoate (entry 9, Table 7):[37] yield 283 mg (87%); white solid; R_f = 0.51 (EtOAc/hexane, 2.0:8.0); mp106−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75−7.73 (d, J = 8.0 Hz, 2H), 7.59−7.57 (m, 2H), 7.40−7.36 (t, J = 8.0 Hz, 2H), 7.31−7.28 (t, J = 8.0 Hz, 2H), 5.34 (br, 1H), 4.39−4.36 (m, 3H), 4.22−4.19 (t, J = 8.0 Hz, 1H), 3.74 (s, 3H), 1.42−1.41 (d, J = 4.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 155.8, 144.0, 141.4, 127.8, 127.2, 125.2, 120.1, 67.1, 52.6, 49.7, 47.2, 18.7; IR (KBr) 3330, 2924, 1747, 1690, 1536, 1267, 1084, 740 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{19}NO_4$ 326.1392, found 326.1388.

DL-Benzyl 2-(tert-butoxycarbonyl)-3-phenylpropanoate (entry 10, Table 7):[38] yield 319 mg (90%); yellowish solid; R_f = 0.50 (EtOAc/hexane, 2.0:8.0); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34−7.31 (m, 3H), 7.28−7.26 (d, J = 8.0 Hz, 2H), 7.24−7.21 (m, 3H), 7.05−7.01 (m, 2H), 5.16 (s, 2H), 5.05 (br, 1H), 4.59−4.54 (t, J = 4.0 Hz, 1H), 3.10−3.07 (d, J = 8.0 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9, 155.2, 136.1, 135.4, 129.5, 128.7, 127.1, 80.0, 67.3, 54.6, 38.4, 28.4; IR (KBr) 3456, 2923, 1732, 1688, 1521, 1223, 1087, 740 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{21}H_{26}NO_4$ 356.1862, found 356.1857.

L-Benzyl 2-(tert-butoxycarbonyl)-3-phenylpropanoate (entry 11, Table 7):[38] yield 316 mg (89%); yellowish solid; R_f = 0.51 (EtOAc/hexane, 2.0:8.0); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36−7.33 (m, 3H), 7.29−7.27 (d, J = 8.0 Hz, 2H), 7.23−7.21 (m, 3H), 7.04−7.02 (m, 2H), 5.14 (s, 2H), 5.01 (br, 1H), 4.63−4.61 (t, J = 4.0 Hz, 1H), 3.11−3.09 (d, J = 8.0 Hz, 2H), 1.41 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8, 155.19, 135.9, 135.5, 129.5, 128.7, 127.1, 80.1, 67.29, 54.6, 38.4, 28.4; IR (KBr) 3456, 2923, 1732, 1688, 1521, 1223, 1087, 740 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{21}H_{26}NO_4$ 356.1862, found 356.1857.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR (^{1}H and ^{13}C) spectra of *o*-NosylOXY, the intermediate, and the products in Table 3 (entries 1−18); Table 4 (entries 1−8); Table 6 (entries 1−13); Table 7 (entries 1−11); HPLC profiles and ESI spectra of peptides; crystal data of the intermediate. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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